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SECOND SERIES VOL. 10, No. 3

BULLETIN

OF

THE NEW YORK ACADEMY OF MEDICINE

INCORPORATED 1851

MARCH, 1934

PUBLISHED MONTHLY BY

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street

New York, N. Y.

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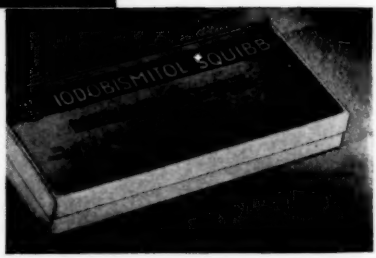

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VOL. 10 MARCH, 1934 No. 3

ANNUAL GRADUATE FORTNIGHT
"DISORDERS OF METABOLISM"
October 23 to November 3, 1933

ACIDOSIS AND ALKALOSIS*

DONALD D. VAN SLYKE

For maintenance of normal physiological function, and of life itself, it is necessary that certain physical and chemical conditions in the body be kept constant within certain limits. Perhaps the most familiar constant of this sort is the body temperature. Ordinarily it is kept within a narrow range. When it deviates from this range changes in physiological functions result, such as the increased metabolic rate, pulse, respiration, and water loss that accompany hyperthermia. When the deviation becomes sufficiently wide, the lethal point is reached, where irreversible changes set in and death follows.

Another such physiological constant is the reaction of the blood. It is normally in the resting man expressed by a pH of 7.4, slightly more alkaline than water. The pH

* Delivered October 25, 1933.

may be raised 0.2 or 0.3 above this level by such a simple physiological means as blowing off carbonic acid in voluntary overbreathing. And it can be lowered as much by the lactic acid produced in the muscles in a short, hard sprint. But if the change goes much farther in the alkaline direction the tetany of alkalosis sets in, nor can much greater change in the acid direction be tolerated without the symptoms of acid poisoning. The range within which life is continuously possible seems to be the narrow zone between pH 7 and 7.8. When we consider that some moulds can grow in 5 per cent sulfuric acid solution, it appears that the efficiency of our complicated and delicate organism has been bought at a heavy cost in cellular hardiness and adaptability.

The acid-base changes in the body are of two types, that caused by excess or deficit of carbonic acid, and that caused by excess or deficit of the supply of buffer alkali available for neutralizing non-volatile acids such as lactic, hydroxybutyric, and hydrochloric. The first type of changes we shall call carbonic acid excess and deficit, the second type we term alkali excess and deficit, because in it the alkali reserve of the body is increased or diminished. Discovery of the occurrence and significance of both types of changes was first made in the physiological laboratory and then found to apply to common clinical conditions. The advance in this field exemplifies the dictum of the elder Haldane: "The physiology of today is the medicine of tomorrow."

Walter in 1877 (50) studied in Schmiedeberg's pharmacological laboratory the effect of administering hydrochloric acid to rabbits. He noted that when 1 gram of HCl per kilo had been administered to rabbits there was great hyperpnea, tachycardia, and collapse, with lowering of the bicarbonate of the blood to nearly zero. Walter made nearly a complete description of the condition which we term *alkali deficit*. A few years later Stadelmann (44) noted "that the symptom complex of diabetic coma greatly resembles that of acid intoxication as revealed by the work

of Walter," and Kussmaul (24) saw the same similarity in the coma of terminal nephritis. These clinical observations led students of disease again back to the laboratory, where Minkowski (32) and Magnus-Levy (29) identified the intoxicating acid of diabetes as beta-hydroxybutyric, and Marriott and Howland (30) and Loeb and Benedict (27) showed that phosphoric acid and sulfuric acids produced in ordinary metabolism are retained in severe nephritis.

The opposite condition, the state of *alkali excess,* was produced experimentally by MacCallum (28), who caused dogs to lose hydrochloric acid from their bodies by ligating the pylorus and washing out the gastric juice. He found a marked increase in the blood bicarbonate, and eventual development of tetany. Since then it has become a common clinical observation that continuous loss of gastric hydrochloric acid by vomiting, whether caused by pyloric obstruction or other factors, results in a state of alkali excess, with a great increase in the bicarbonate of the blood and a decrease in the chloride.

The acid-base changes due primarily to respiratory over- or underventilation were also first noted in physiological experiments, and quickly found to be not unusual clinical occurrences. Grant and Goldman in 1920 showed that by voluntary overventilation they could produce an alkalosis of *carbonic acid deficit,* with development of tetany quite like that produced by loss of HCl or overdosage with sodium bicarbonate. A similar overventilation was soon observed by Harrop and Loeb (16) in encephalitis, has been found to be not uncommon in hysteria, and to a milder degree has been noted by Koehler (22) to be frequent in febrile conditions generally.

The tetany which accompanies the alkalosis of either alkali excess or CO_2 deficit appears to be connected with the pH increase in the blood, which occurs in both conditions. The symptoms are the same as in the tetany produced by lack of blood calcium. They occur when the pH exceeds 7.6-7.7, even though the calcium content is normal.

The acidosis of *carbonic acid excess* was produced in 1914 by Hasselbalch and Lundsgaard (19a), who caused animals to breathe air containing CO_2, so that the concentration of free carbonic acid in the blood was increased. There was a marked depression of the blood pH, and a great hyperpnea, similar to that observed in Walter's experiments, in which the retained acid was hydrochloric. Later Dautrebande (7) and Meakins (31) found that there is a similar retention of CO_2 in some cases of emphysema and bronchitis, in which gas exchange in the lungs is markedly hindered, and in such cases dyspnea is present or readily produced by slight exertion.

The Blood Bicarbonate and Its Relation to the Available Buffer Alkali of the Body

The physiologically available alkali reserve of the body is in the form of buffer salts. These have the power of forming solutions, which with relatively little pH change, are able to neutralize the greater part of the acidity or alkalinity of added strong acids or alkalies. The manner in which buffers act is illustrated by the behavior of bicarbonate to which HCl is added. The reaction occurs:

$$NaHCO_3+HCl=H_2CO_3+NaCl$$

The effect is to replace the strong acid, HCl, with an equivalent of a weak acid, H_2CO_3, so that the hydrion concentration in the mixture of $NaHCO_3$, H_2CO_3, and NaCl is only a minute part of that which would exist if the HCl had remained free.

If, on the other hand, alkali instead of acid is added to a solution containing $NaHCO_3$ and H_2CO_3, the alkali reacts with the H_2CO_3 component:

$$NaOH+H_2CO_3=NaHCO_3+H_2O$$

In consequence the strongly alkaline NaOH is replaced by the weakly alkaline $NaHCO_3$. Thus a solution containing the buffer mixture, $NaHCO_3$ and H_2CO_3, can receive either strong acid or strong alkali with relatively small change in pH.

The neutralization of an acid or alkali by a buffer is not complete in the sense that the pH of the buffer solution remains entirely unchanged. If HCl, for example, is added to a $NaHCO_3$-H_2CO_3 mixture, the H_2CO_3 is increased and the $NaHCO_3$ is diminished, so that the pH becomes somewhat more acid, but the change is only a small fraction of what it would be if the HCl were added to an unbuffered solution (For a more complete account of the action of buffers, see [45*a*]).

In the body it is true that $NaHCO_3$ can almost completely neutralize invading acids, for the reason that the lungs can blow off the H_2CO_3 formed by reaction of the invading acid with bicarbonate. For the reason that its acid component can thus be removed almost instantly from the body, bicarbonate as a buffer offers a unique advantage over other buffers in the blood and tissues.

In the blood the chief part of the buffers is in the form of bicarbonate, the concentration of which is about 0.02 molar. About 0.01 equivalent more of alkali is available in the form of alkali hemoglobinate, which may be most simply symbolized as BHb. With these two buffers the 5 liters of blood in the body contain buffer alkali enough to absorb nearly 0.15 mole, or 150 c.c. of normal HCl, before the reaction becomes fatally acid. But the chief alkali store in the body is in the buffers of the tissues, which can neutralize about 5 times as much acid as the buffers of the circulating blood (46).

Although the blood bicarbonate contains only about 0.1 of the total available buffer alkali of the body, nevertheless it indicates the condition of the entire supply. For when an invading acid exhausts part of the blood buffer alkali with a fall in blood pH, the effect is divided with the buffers of the tissues bathed by the blood, so that the alkali reserve of all goes up and down together. The blood bicarbonate accordingly serves to indicate the state of the total alkali reserve of the body.

It has become customary to speak of the blood bicarbonate itself as the "alkali reserve." It is, in fact, a measuring-stick for the total reserve of the body, and as such the term "alkali reserve" may be applied to it.

In two other respects the bicarbonate and free carbonic acid of the blood have an especial significance. They are directly related on the one hand to the activity of the pulmonary respiration, and on the other to the actual reaction, the hydrion concentration or pH, of the blood. A 0.01 M solution of H_2CO_3 has an acid reaction, approximately pH 4, while a 0.01 M solution of $NaHCO_3$ has a definitely alkaline reaction of pH about 8. A solution with equal concentrations of both H_2CO_3 and $BHCO_3$ will have the intermediate pH of 6.1. The pH of any given mixture of H_2CO_3 and $BHCO_3$, in the presence of a physiologically normal concentration of total salts, depends on the ratio of $BHCO_3$ to H_2CO_3, as indicated by the Henderson-Hasselbalch equation (20):

$$pH=6.1+\log\frac{BHCO_3}{H_2CO_3}$$

(B=any base, Na, K, etc.). In the normal blood plasma $\frac{BHCO_3}{H_2CO_3}=\frac{20}{1}$ and the pH is 7.4.

Because of the relationship of the blood bicarbonate to the available buffer alkali supply of the body, to the respiratory regulation of the H_2CO_3, and to the vitally important pH of the blood, study of the blood bicarbonate gives more information about the state of the body's acid-base economy than observation of any other one value which can be easily determined. If the bicarbonate determination is coupled with that of the plasma pH, information is afforded which enables one to state whether the acid-base balance of the organism is normal, and if it is not, to diagnose whether the deviation is due to excess or deficit of alkali, or to respiratory loss or retention of CO_2.

The CO_2 Absorption Curve and the Acid-Base Diagram

The buffer alkali of the blood is partly combined with carbonic acid, and partly with hemoglobin, which acts also as a weak acid. When H_2CO_3 is present in ordinary concentrations, about 2/3 of the buffer alkali takes the form of $BHCO_3$, and 1/3 that of BHb. But if CO_2 escapes from the blood, so that the H_2CO_3 content decreases, some of the base shifts from $BHCO_3$ to the form BHb, in accordance with an approximate mass law equation:

$$\frac{BHCO_3}{BHb} = \frac{H_2CO_3}{HHb}$$

If ordinary blood is aerated so completely that all the free carbonic acid is removed, the bicarbonate completely disappears, all the buffer alkali shifting to the form BHb. Consequently, when the bicarbonate is determined as an indicator of the state of the acid-base condition of the body, it is necessary that the H_2CO_3 content of the blood be at a normal, or at least a known, concentration.

The behavior of the total CO_2, the $BHCO_3$, and the H_2CO_3 of the blood when the pressure of CO_2 in the atmosphere saturating the blood is varied, is shown by the carbon dioxide absorption curve in Figure 1. This type of curve was introduced by the elder Haldane for such studies of the blood, and is almost indispensable for graphic explanation of the conditions. It is seen that when the CO_2 tension, and the proportional concentration of dissolved free carbonic acid, represented as H_2CO_3 in the lowest slanting line, fall to zero, the total CO_2, including the $BHCO_3$, also falls to zero. At this point all the buffer alkali in the blood is in the form of alkali hemoglobinate, and a CO_2 or bicarbonate determination would lead to an interpretation that the alkali reserve had disappeared. It is only when the blood $BHCO_3$ or CO_2 content is determined with the CO_2 tension at a normal level that the $BHCO_3$ or total CO_2 content has significance as an accurate indicator of the acid-base balance of the blood and the alkali reserve of the body.

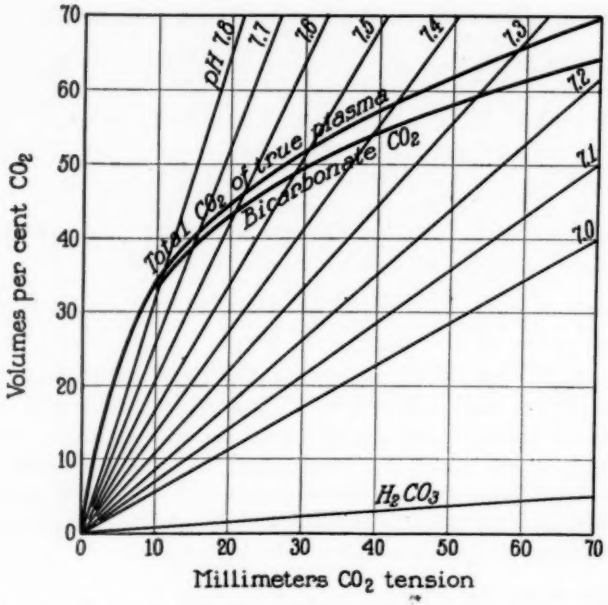

Fig. 1. Carbon dioxide absorption curve of true plasma of normal human blood. The ordinates represent the CO_2 content of plasma separated after the blood has been saturated with air containing CO_2 at the tensions indicated by the abscissae.

It may be desirable here to interject a word of explanation concerning the significance of the CO_2 tension and its relation to the H_2CO_3 content of the blood. The term "CO_2 tension" is used to express concentration of CO_2 in the air with which the blood is saturated. The total pressure or tension of the gases in air at average sea level barometric pressure is 760 mm. of mercury. If dry air contains 5 per cent of CO_2 the tension of CO_2 is 0.05 of 760 or 38 millimeters. When blood plasma is saturated at body temperature with pure CO_2 at 760 mm. tension, the plasma dissolves 51 volumes per cent of CO_2 as free carbonic acid, which is symbolized as H_2CO_3. If the CO_2 tension of the saturating gas is 40 mm., as it ordinarily averages in the alveolar air, the plasma H_2CO_3 content is

$\frac{40}{760} \times 51 = 2.7$ c.c. per 100 c.c. of plasma, or 2.7 volumes per cent as ordinarily expressed. The free carbonic acid content, H_2CO_3, of the blood is therefore dependent on the CO_2 tension of the air with which the blood is saturated.

In the case of arterial blood, this air is that of the pulmonary alveoli. If one breathes more deeply and rapidly than usual the CO_2 of the alveolar air becomes more diluted; in other words its tension falls, and the H_2CO_3 of the blood falls proportionally. The point which represents the condition of the blood on the CO_2 absorption curve of Fig. 1 then moves from its normal place, corresponding to about 40 mm. of CO_2 tension, to a place further to the left. As the result of the decrease in H_2CO_3 the $BHCO_3$ content of the blood becomes lower, some of the base being changed from bicarbonate to the form of alkali hemoglobinate, BHb. Such a change is merely a respiratory one, and does not indicate any change in the supply of available buffer alkali. A decrease in the alkali reserve, such as would be caused by addition of lactic or hydrochloric acid to the blood, would be shown by a fall in the level of the entire CO_2 absorption curve. That is, with a normal CO_2 tension the amount of base free to form bicarbonate would be decreased. In general, *acid-base changes due to respiratory retention or blowing off of CO_2 are shown by movements back and forth on the CO_2 absorption curve, while changes due to loss or retention of non-volatile acids, or of alkali, are shown by rise or fall of the level of the entire curve.*

The slanting straight lines drawn from the origin across Fig. 1 represent pH values calculated by the Henderson-Hasselbalch equation. They enable one to visualize the manner in which the blood pH changes in conditions of CO_2 excess and deficit, and of alkali excess and deficit.

A somewhat more convenient way of charting the CO_2 absorption curve was introduced by J. P. Peters (39), and is shown in Fig. 2. It is the same as Fig. 1, except that the CO_2 tension and CO_2 content values are laid off in logarith-

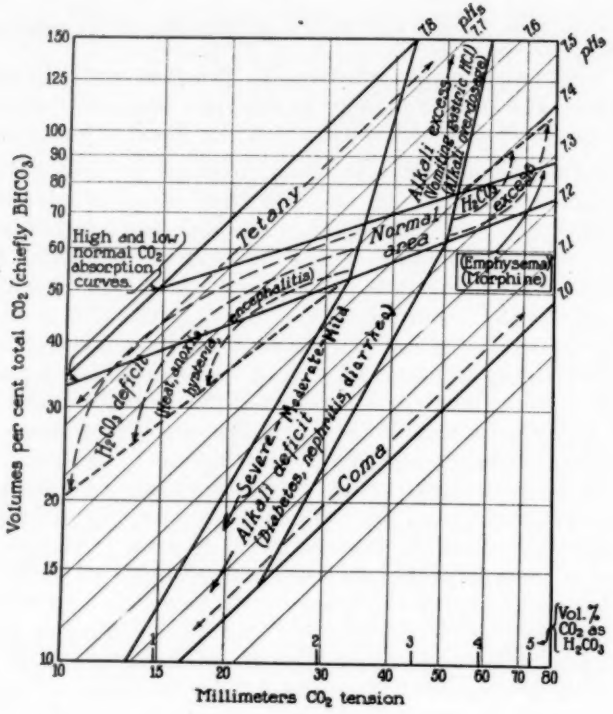

Fig. 2. Changes in CO_2 content, H_2CO_3 content, CO_2 tension, and pH of the blood plasma in conditions of carbonic acid excess and deficit, and of alkali excess and deficit. A point located in the wedge-shaped area between two fields indicates a mixture of the conditions indicated by the adjacent fields.

mic scales, the intervals denoting 1 volume per cent of CO_2 content or 1 mm. of CO_2 tension becoming greater for lower CO_2 values. The convenience of this form of chart is that the pH lines become parallel, and the CO_2 absorption curves, above 10 mm. of CO_2 tension, become nearly straight lines. We shall use this chart to illustrate the changes that occur in conditions of H_2CO_3 excess and deficit, and of alkali excess and deficit.

The chart expresses values of the plasma centrifuged from the blood, rather than of the whole blood. The reason for preferring plasma values is that CO_2 content in the cells is only about 0.6 as great as in the plasma. Consequently, in a series of bloods which all have an identical average normal acid-base balance as indicated by plasma bicarbonate and pH, but in which the proportions of cells and plasma are different, the anemic bloods will show higher than average normal whole blood CO_2 contents, which might be interpreted to indicate alkali excess, while the polycythemic bloods will show the reverse.

Carbonic Acid Excess

Causes. This condition is of respiratory origin and is due to conditions which prevent a normally efficient aeration of the blood in the lungs. It occurs when anatomical changes in the lungs interfere with aeration of the pulmonary blood, or when the respiratory center is dulled, so that breathing is retarded.

Experimentally it can be produced by breathing air containing 4 or 5 per cent of CO_2, or simply by holding the breath, or by the mechanical interference of partial tracheal obstruction. It is also caused by morphine administration, which deadens the respiratory center.

Clinically the condition has been identified by Meakins (31) and Dautrebande (7) in emphysema and in conditions of bronchitis and asthma in which pulmonary gas exchange is interfered with. In asthma and bronchitis it is probable that passage of air into the alveoli is retarded by contraction of the bronchi and bronchioles, while in emphysema the retarding changes are presumably in the alveoli. In morphine poisoning carbonic acid excess occurs (21) and is attributable to deadening of the respiratory center. In Cheyne-Stokes breathing it occurs momentarily during the periods of apnea (1).

Effects of carbonic acid excess. The effect on the acid-base condition in the blood is indicated by the "H_2CO_3 Excess" area in Fig. 2. The point representing blood conditions is immediately displaced by CO_2 retention, and moves to the right along the CO_2 absorption curve of the particular blood in question. The direction of the movement is indicated by the arrows to the right of the normal area. There is an increase in the CO_2 tension and a decrease in the pH in this CO_2 acidosis. The alkali reserve is at first not affected, but after some hours of carbonic acid excess a compensatory increase in the alkali reserve sets in, shown by the upward curve of the arrows towards their points. This increase was demonstrated by Yandell Henderson and Haggard (21) in experiments on dogs, and was noted by Dautrebande in the emphysematous patients whom he examined. In such cases, in which the condition is chronic, the points indicating the blood condition are found near the tips of the arrows in this area on the chart, above the level of ordinary CO_2 absorption curves. The increase in alkali reserve is presumably caused by the increased urinary excretion of acid, in titratable form and as ammonium salts, which accompanies the H_2CO_3 excess.

The only subjective symptom attributable to the condition is the exertion dyspnea, which is seen in subjects such as emphysematous patients, in whom the H_2CO_3 retention is due to pulmonary mechanical interference. Such individuals do not, even while at rest, ventilate their lungs well enough to prevent some H_2CO_3 increase in the blood. And when CO_2 formation in the body is increased by exercise, the carbonic acid retention quickly increases. There is a maximum effort to blow off the retained carbon dioxide, but it is only partly successful, and the patient has the same feeling of distress that is produced by holding one's breath.

Clinically the condition of carbonic acid excess is not in itself serious. As will be seen from Fig. 2, the decrease in pH is slight, and after compensatory increase in alkali

reserve has occurred the H_2CO_3 retention may be quite balanced by the increased $BHCO_3$, so that the pH returns to normal. Much more important than the acid-base alteration in such cases is the oxygen lack that threatens the organism. As shown by the Danish physiologist, Krogh (23), oxygen diffuses many times more slowly than carbon dioxide through membranes. Consequently whenever there is CO_2 excess from pulmonary malformations or from deadened respiratory center, there is a still more marked oxygen deficit in the arterial blood (18). Emphysematous patients who have sufficient CO_2 retention to be dyspneic also as a rule have so much arterial anoxemia that they are cyanotic.

The amount of CO_2 acidosis that occurs will never damage the patient, but the anoxia may readily reach the same stage which at high altitudes causes distress even to normal subjects. The CO_2 retention, in fact, is probably beneficial in such cases, because the excess of H_2CO_3 and the consequent slight decrease in blood pH stimulate the respiration, and thereby cause the anoxia to be less severe than it would with a normal acid-base balance. Furthermore the dyspnea, which results in such patients from increased excess H_2CO_3 when they exercise, is doubtless a salutary check to prevent them from undertaking exertions for which their lungs can not supply the necessary oxygen.

Carbonic Acid Deficit

Causes. This condition results when ventilation is so stimulated that CO_2 tension in the alveolar air and the blood is reduced below the level required to maintain the usual pH in arterial blood. The $BHCO_3 : H_2CO_3$ ratio increases because the denominator becomes smaller, and in consequence the pH rises. The condition is one of respiratory alkalosis.

The respiration is as a rule so regulated that the alveolar and arterial CO_2 tensions and the pH are kept within the limits indicated by the normal area in Fig. 2. The lungs,

however, also serve other functions: they oxygenate the blood, and at times their assistance is needed in cooling the body. When need for either of these functions becomes great, that need partially usurps control of the respiratory rate, which is accelerated with a certain amount of disregard for maintenance of normal pH. In consequence the blood pH may rise so high, as indicated in Fig. 2, that tetany results.

Experimentally this condition can be readily produced, as in Grant and Goldman's work, simply by voluntary overbreathing for some minutes. Bazett (2) produced it to the point of tetany by immersing the body in a hot bath, so that ventilation of the lungs was the only channel for escape of bodily heat. To a lesser degree hyperventilation occurs in high altitudes, where the oxygen concentration of the air is diminished and increased respiration is needed to maintain oxygenation of the blood.

Clinically a mild degree of alkalosis from carbonic acid deficit has been noted in fevers due to various causes (Koehler [22]), and a more severe form has been observed in some cases of encephalitis, in which the condition may approach tetany (Harrop and Loeb [16]). In this disease it appears that the central nervous infection may cause a state of hyperirritability of the respiratory center. Nervous or hysterical individuals sometimes overbreathe merely as the result of excitement, and may continue until symptoms of tetany appear.

Effects of carbonic acid deficit. The first effect of such hyperpnea is to lower the CO_2 tension and in consequence raise the pH in the blood. The point representing in Fig. 2 the condition of the plasma moves to the left from the normal area. The height of the CO_2 absorption curve, and therefore the alkali reserve, are not changed for some time. However, as the apparent result of the increased pH of the blood, the acid excretion in the urine is replaced by alkali excretion, and the alkali reserve of the blood begins a gradual fall. The point representing the acid-base

balance of the plasma then follows the downward curve of the arrows in the "H_2CO_3 deficit" area of Fig. 2. The effect of diminishing the alkali reserve is to decrease the $BHCO_3$ and lower the pH part way back towards normal. The diminution of the alkali reserve is regularly noted in men who go to high altitudes, and appears to reach a limit after a few days residence there. The fall in alkali reserve appears to be almost directly proportional to the fall in barometric pressure (8), and may be great enough to bring the bicarbonate content down to the region indicated by the broken line at the bottom of the CO_2 deficit area in Fig. 2.

Treatment of carbonic acid deficit. The most serious symptom that can be attributed to carbonic acid deficit is the tetany. The drug which has been found to quiet the respiratory center, and which should therefore serve to combat the condition, is morphine. Other sedatives appear not to have been investigated.

Alkali Excess

Causes. This condition can arise from either of two causes: (1) Alkali buffer salts may be absorbed, either as such ($NaHCO_3$, Na_2HPO_4), or as alkali organic salts (sodium acetate or citrate) of which the organic radicle is burned, forming bicarbonate in the body. (2) The body may lose acid, as by vomiting gastric HCl. In either case the effect is to increase the reserve of buffer alkali in the body, since the excess of base over strong acids automatically divides itself between bicarbonate and the other buffers.

Effects of alkali excess. The symptoms referable to the acid-base disturbance in both cases are similar. The blood bicarbonate and pH increase, and if the condition goes far enough tetany of alkalosis may occur. The history is usually sufficient to indicate whether the condition is due to alkali dosage or to loss of gastric HCl. Also, when it is due to retention of alkali salts, the excretion of bicarbonate in the urine may be several grams per hour. Whereas if loss of

gastric juice is the cause there is so great a loss of salts from the body that the bicarbonate is held back by the kidneys in the apparent attempt to preserve the total salt content of the body fluids. The urine in alkalosis caused by loss of gastric HCl is usually alkaline and contains some bicarbonate, but in smaller amounts than those excreted after alkali overdosage; and the urine may even remain acid (17). There is also as a rule a marked dehydration of the body when the alkalosis is due to loss of gastric juice, because sodium chloride and water are lost with the HCl, whereas retention of administered alkali is likely to be accompanied by water retention rather than by dehydration.

The effects of alkali excess on the urine are usually to make it alkaline, diminish the ammonia to almost zero, and cause excretion of bicarbonate, which in amount is dependent on the origin of the condition, as indicated above. The sum of ammonia and titratable acid in the urine usually approaches zero when the plasma CO_2 rises to 75 or 80 volumes per cent.

Treatment of alkali excess. When the condition is due to administration of alkali salts no treatment appears to be necessary. The kidneys excrete bicarbonate and retain acid radicles, and rapidly restore the blood to normal condition.

When the alkali excess is caused by loss of gastric HCl, such as occurs in toxic vomiting and pyloric or intestinal obstruction, the treatment found efficacious has been administration of salt and water (11). The absorbed saline solution corrects the dehydration, which is probably the most serious factor in this condition, and as soon as the total salt content of the body fluid has been restored the kidneys excrete the excess of bicarbonate and restore the acid-base condition to normality. Administration of acid or acidifying salts does not appear to be necessary.

Alkali Deficit

This is the acid-base abnormality which is of the most clinical importance, and we shall therefore discuss it somewhat more fully than the foregoing types. It is the condition encountered in the acidoses of diabetes, of diarrhea and of nephritis.

Causes

Alkali deficit can arise from either of two causes: (1) Alkali may be lost from the body in the form of bicarbonate, which is the only form in which significant amounts of base appear to leave the body without equivalent amounts of fixed acids. (2) Non-volatile acids, such as lactic, hydroxybutyric, or hydrochloric, may be retained in the body, and exhaust equivalent amounts of buffer alkali. Either of these causes is capable of producing severe acidosis of the alkali deficit type.

1. *Loss of alkali bicarbonate from the body.* In severe diarrhea it appears that large amounts of alkali bicarbonate can leave the body by way of the intestine. Gamble and McIver (10) have shown that the salts of bile and pancreatic juice consist chiefly of alkali bicarbonate. It appears probable that loss of this bicarbonate is the cause of the acidoses that occur in the diarrheas of infants, and of cholera in adults (Peters and Van Slyke, p. 980 [40]).

Theoretically, it should be possible to produce a similar loss by a combination of achylia gastrica and intestinal obstruction so located that bile and pancreatic juice would be vomited. Actually, however, it does not appear that alkali deficit from this cause has ever been observed, nor as yet produced experimentally. In the cases of intestinal obstruction and fistula reviewed by Walters, Kilgore and Bollman (51) the loss of gastric HCl has been more important than the loss of alkaline secretions from the intestinal juice. The result has been, not alkali deficit, but alkali excess in the blood, such as we have noted in connection with loss of gastric HCl in pyloric obstruction. The only difference observed has been that the alkali excess

appears to develop less rapidly as the obstruction or fistula is farther down the intestine.

The kidneys excrete significant amounts of bicarbonate only when there is a state of alkalosis, due either to alkali excess or to carbonic acid deficit, two conditions which we have already discussed. When the acidosis of alkali deficit occurs, the urine becomes acid, alkali excretion stops and is replaced by excretion of acid in the form of ammonium salts and titratable acid. Urinary loss of alkali may be excluded as a cause of internal alkali deficit.

The one important path of alkali loss from the body appears to be by way of diarrheal discharges.

2. *Retention of fixed acids.* (The term "fixed acids" is used to indicate acids other than carbonic.) This is the most frequent cause of alkali deficit in adults. For example, the lactic acid acidosis of exercise, the acidoses produced by retention of phosphoric and sulfuric acids in nephritis and by retention of ketone acids in diabetes, and in the explosive ketoses of children. In each of these cases some endogenous acid is formed more rapidly than it is removed by chemical destruction or excretion. Hence the name *acidosis* was originally applied to states of alkali deficit.

Experimentally, alkali deficit from acid retention can be produced by severe exercise or anoxia (lactic acid retention), by administration of mineral acids, as in Walter's experiments, or by oral administration of ammonium, calcium, magnesium, or strontium chloride. The ability of these "acidifying salts" to lower the alkali reserve was discovered by J. B. S. Haldane (12, 13). The ammonia salts are absorbed, and the ammonia is changed to urea, setting free the HCl of the NH_4Cl. Ammonium sulfate and nitrate act similarly. When the Ca, Mg, or Sr chloride is given, the cation is excreted from the intestine and the HCl retained. Because of the diuretic effect of acid retention, these salts may be used as diuretics in conditions where some loss of alkali reserve can be tolerated.

Effects of Alkali Deficit

In the blood the bicarbonate content and pH are at once lowered, as the result of decomposition of $BHCO_3$ by the invading acid (See Fig. 2).

Respiration accelerates, so that the CO_2 formed from the decomposed bicarbonate is blown off, and hyperpnea then continues at a sufficient rate to keep the H_2CO_3 content of the blood lower than normal, so that the pH does not remain so low as it would have been without this hyperpnea. The respiratory acceleration is, however, not so great relatively as the fall in blood $BHCO_3$; if it were, the $BHCO_3$:H_2CO_3 ratio and hence the pH would remain entirely normal. For example, if CO_2 in the form of plasma $BHCO_3$ fell from 60 to 30 volumes per cent, and respiration doubled so that the CO_2 tension also fell to half (from 40 to 20 mm.) it is apparent from Fig. 2 that pH would remain constant at 7.42. On the other hand, if there were no respiratory acceleration at all, CO_2 tension would remain at 40 mm., and pH would fall to 7.1. What ordinarily happens, as indicated by the path of change on the diagram, is a compromise. There would be, in the example cited, enough hyperpnea to lower the CO_2 tension to about 30 millimeters, so that the pH falls only to about 7.25 instead of 7.10. Respiration would then remain at about 1/3 above the normal resting rate, e.g., raised from 5 liters per minute to 7 or 8. At this level the respiration would be maintained, apparently by the effect of the increased hydrion concentration of the blood on the respiratory center (15, 52).

There are, as we have shown, other factors, such as heat, outside of the acid-base balance which affect respiration, but the acid-base factor in the blood which under ordinary conditions has chief control appears to be the pH.

It is true that H_2CO_3 excess also causes hyperpnea, but the stimulant appears to be the increased hydrion activity. If it were the H_2CO_3 we should not have the picture seen here in alkali deficit, where there is hyperpnea with *less than normal CO_2 tension and H_2CO_3 concentration.*

In extreme alkali deficit, when the plasma pH is lowered to 7 or below, the hyperpnea may be the most striking feature of the entire clinical picture. Respiration may reach its mechanical limit, with the fearful air-hunger described by Kussmaul.

The circulation responds with an increased pulse rate. Tachycardia was one of the effects first noted in Walter's classic experiments.

On *renal excretion* the effect varies according to the cause of the alkali deficit.

When the cause is retention of fixed acids, such as the ketone acids in diabetes, or of HCl or other mineral acids given by mouth as free acids or as calcium or ammonium salts, the kidneys react with an elimination of the invading acid in the form of its alkali salts produced by decomposition of body bicarbonate. If the acidosis continues and the supply of buffer alkali decreases, ammonia formation by the kidneys greatly accelerates, and increasing amounts of the invading acid are eliminated as ammonium salts. With the salts of the foreign acid the kidneys, with apparent temporary loss of discrimination, excrete some of the body's supply of sodium chloride. With the salts goes an equivalent volume of the body fluid. Acidosis of this type therefore has a powerful diuretic effect, and results in dehydration of the body from loss of its saline fluids. This dehydration in diabetic acidosis may be so great that it contributes seriously to the state of collapse.

When the cause of the alkali deficit is alkali loss in diarrheic stools, the effect on the urine is not diuresis but oliguria. The salt and water loss through the intestine is so great and produces such rapid desiccation of the body that the diuretic influence of the acidosis is quite overcome. The urine volume may become so small that retention of nitrogen occurs, and symptoms of uremia.

After one or more days of severe alkali deficit, either from acid retention or from alkali loss, there is usually a

dehydration of the body. If body saline fluids have not been lost through the intestine they have been wasted through the kidneys. For this reason, *treatment of severe alkali deficit usually calls for administration of salt and water to replace fluid loss as well as of alkali to restore the alkali reserve.*

Defense Reactions of the Organism Against Alkali Deficit

These reactions appear generally to rank as follows with regard to the rapidity with which they begin effective work against the threatened acidification of the body.

1. The *buffers* of the body neutralize the invading acid. This reaction is instantaneous, as soon as the acid comes into contact with the buffers in the blood and the tissues. As we have stated, it is estimated that in an adult man the blood contains enough buffers, as alkali bicarbonate and hemoglobinate, to neutralize about 150 c.c. of N/1 acid, and the rest of the body enough additional buffers to bring the total tolerance of invading acid up to about 1 liter of N/1 acid.

2. The *lungs* drive off the CO_2 that has been formed by decomposition of body bicarbonate. They furthermore increase their ventilation rate, so that not only the newly formed H_2CO_3 is removed, but also part of the pre-existing H_2CO_3. In consequence, as we have shown, the $BHCO_3$:H_2CO_3 ratio and the pH do not fall so far as they would if the $BHCO_3$ were lowered while the H_2CO_3 remained constant (Fig. 2).

3. The *kidneys* begin to excrete acid phosphate, and in diabetic acidosis, free hydroxybutyric acid. They thereby diminish the acid retention. Later the kidneys begin to excrete more than usual amounts of ammonia, and if the acidosis continues ammonia formation becomes the chief defense against it.

Excretion of acid phosphates sets in at once, and assists in combating the loss of alkali reserve. J. B. S. Haldane (14) showed that the excreted phosphoric acid is in part at least derived from the organic phosphoric esters of the blood, which greatly diminish during the first days of experimental acidosis.

With continuance of the acid invasion, the phosphate excretion becomes retarded, apparently because of exhaustion of the supply of organic phosphates, and *ammonia excretion* becomes important. In quickly induced experimental acidosis ammonia excretion may be very little accelerated during the first day, even though the blood bicarbonate falls to less than half the normal value and the pH to 7.1-7.2 (Følling, 9). It is only later, after the supply of readily excretable base and phosphate is diminished, that ammonia formation greatly increases. (When the acidosis is caused by administration of acid phosphate Marriott and Howland (30) showed that no increased ammonia output occurs.) The excreted ammonia, as shown by Nash and Benedict (33), is formed in the kidneys. It enables the body to eliminate the invading acid as its ammonium salt, and to spare the alkali reserve. The end results of the procedure may be represented by the reaction:

NH_4HCO_3	+	NaA	=	NH_4A	+	$NaHCO_3$
formed from urea in kidney		salt of invading acid		excreted		retained in blood

If the kidneys are diseased ammonia formation may fail to increase. Consequently, as shown by Rabinowitch (41), there is more danger of acid intoxication in diabetes if nephritis is also present. In severe nephritis ammonia formation diminishes (35, 47). Even if acidosis is present the ammonia output may be less than the usual normal.

In diabetic acidosis it happens that the chief invading acid, *hydroxybutyric,* is such a weak organic acid that at the most acid reaction of the urine, about pH 5, nearly half of this *acid can be excreted in the free form,* with-

out neutralization by ammonia or body alkali. In no other type of clinical alkali deficit, however, does it appear that the invading acid is weak enough to be excreted to an important extent in the free form. The organism must rely upon ammonia formation to restore its alkali reserve.

Even in diabetic acidosis, ammonia formation is ordinarily the chief means by which the invading acid is prepared for excretion. In severe cases the ammonia excretion in 24 hours may be equivalent to 600 c.c. of N/1 solution, while the maximum free acid output is only about ¼ as much.

4. When the invading acid is organic, *combustion* may remove it as soon as conditions permit. In diabetic acidosis combustion can be accelerated by administration of insulin and glucose. In the lactic acid retention following severe exercise or intense anoxia combustion occurs quickly when the muscles rest or the blood is again adequately oxygenated.

Treatment of Alkali Deficit

When the plasma CO_2 is below 50 volumes per cent, with decreased or normal pH, there is alkali deficit, but it is too mild as a rule to require alkali therapy unless the CO_2 is below 40 volumes per cent (45). Obvious symptoms, such as hyperpnea and drowsiness, are usually not marked until the CO_2 falls below 30. When this point is reached the condition may be considered severe, and therapy is usually advisable.

The general therapy for alkali deficit remains alkali administration, as recommended fifty years ago by Stadelmann. But experience has shown fluid loss to accompany alkali deficit so frequently that administration of sodium chloride and water is almost regularly required with the alkali therapy. The administration is preferably oral when the alimentary tract will absorb it and the need is not urgent. But in severe diabetic acidosis the need may be urgent, and in the severe diarrheas of cholera and of infants

there is both urgency and intestinal intolerance. Intravenous injection is then indicated, at least for the first treatments.

By mouth alkali may be given in the form of bicarbonate, citrate, or acetate of sodium. The organic radicles of the citrate and acetate are burned, so in the body these salts are turned into bicarbonate.

For intravenous injection, sodium bicarbonate alone has thus far been ordinarily used. An isotonic solution of it contains 13 grams per liter. If the solution is first prepared and then sterilized by heat, it turns intensely alkaline from loss of CO_2, and the reaction must be restored by running a stream of carbon dioxide through the solution until it is no longer red to phenolphthalein. However, a more convenient way was introduced by Rogers (42), who sterilized the solid bicarbonate by dry heat in packages, and then dissolved it in sterile water or saline solution.

The amount of bicarbonate required to restore a normal alkali reserve can be calculated from the CO_2 content of the blood plasma (Palmer and Van Slyke [38]). The rises in plasma CO_2 and bicarbonate concentrations are approximately what they would be if the bicarbonate were added to a volume of fluid containing 0.7 liter for each kilo of body weight. The amounts required to raise the alkaline reserve to the point indicated by 60 volumes per cent of plasma CO_2 content, or 25 millimoles of $BHCO_3$, and pH 7.4 are indicated by the line chart on Fig. 3.

When injections are given it is well to calculate both the amount of bicarbonate required to restore a normal alkaline reserve and the volume of fluid required to restore that lost from the body, as nearly as this can be estimated from the loss in body weight or otherwise. To the volume of isotonic bicarbonate solution required to restore the alkali reserve is added the volume of 0.9 per cent NaCl solution required to make a total volume sufficient to replace the lost body fluids. When large amounts are required, the infusion is made in portions at suitable time intervals apart.

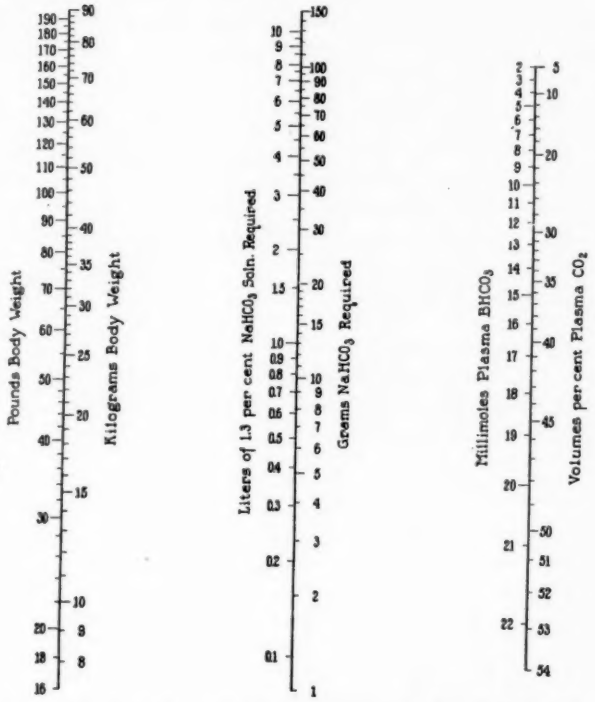
Pounds Body Weight
Kilograms Body Weight
Liters of 1.3 per cent NaHCO3 Soln. Required
Grams NaHCO3 Required
Millimoles Plasma BHCO3
Volumes per cent Plasma CO2

Fig. 3. Line chart for estimating the amount of sodium bicarbonate required in conditions of alkali deficit to raise the CO_2 content of the plasma to 60 volumes per cent or the $BHCO_3$ content to 25 millimoles per liter. A straight line cutting the scales for body weight and plasma CO_2 or $BHCO_3$ content will cut the middle scale at a point indicating the bicarbonate administration required.

The efficacy of such treatment in a condition complicated by extreme loss of both alkali and fluid is indicated by the results of Rogers (42) with Asiatic cholera; the mortality of severe cases treated with infusions of bicarbonate and salt was only one-fourth the mortality of similar cases not so treated. Rogers added 0.5 gm. of calcium chloride (presumably $CaCl_2.6\ H_2O$) per liter to his $NaHCO_3$-NaCl infusions. The Ca concentration was about 2.5 millimolar, the same as in normal plasma. Cal-

cium addition seems logical in treating alkali deficit caused by diarrhea, because there is likely to be also calcium deficit, due to losses in the stools.

When severe acidosis was first noticed as a complication of the diarrheas of infants about 20 years ago, and bicarbonate therapy for the condition was introduced, the usual result was relief of dyspnea and temporary improvement, but death nevertheless. At that time the importance of treating also the dehydration factor was not realized. Salt was not given with the bicarbonate, and the bicarbonate itself was given in concentrations of 4 or 5 per cent: that is, with only one-third enough water to make an isotonic solution. Since then, however, Marriott, Schloss, and other pediatrists have pointed out the necessity of restoring lost salt and water, as well as alkali, and more cases are saved.

In the *acidosis of severe nephritis* alkali therapy may for a few hours restore a comatose patient to consciousness, but it is impossible to eliminate the retained and continually forming acid products, and it appears doubtful that the treatment prolongs life to a significant extent. It may, however, afford relief from the air hunger. In some cases dehydration and depletion of body NaCl are such that benefit is gained by saline infusions, but in other cases nephritic edema or cardiac edema is present to contraindicate saline treatment.

Special treatment of diabetic acidosis. In the days before insulin the treatment of a severe diabetic acidosis was an art demanding high skill and only to a certain extent definable by rules. The technique developed by Dr. Edgar Stillman (45) approached, I believe, the limit of success that was then attainable. Bicarbonate was given slowly by mouth, at the rate of about 3 grams per hour. Abundant fluids, with some salt, were given to obtain a free flow of urine and correct dehydration. Food was administered as it could be tolerated. The conditions of shock, chill, and dehydration, as well as the acidosis had to be combatted, and the patient so managed that the fluids and food given did not cause nausea, which might nullify the results of

hours of treatment. Acids were sometimes formed almost as rapidly as bicarbonate could be taken, so that 40 or 50 grams of bicarbonate on each of several successive days had to be given. In such cases the freshly formed acids made the eventual alkali administration much greater than that calculated from the plasma CO_2 at the beginning. The changes in alkali reserve had to be followed by repeated blood analyses. It sometimes required as much as 36 hours of minute attention to bring a patient back from the verge of coma, and several days to approach a normal alkali reserve, but Stillman proved that it could be done even in severe cases.

With insulin the problem is greatly simplified, and you have heard the technique of combined administration of insulin, glucose, and saline solution discussed so frequently that there is nothing to be added. The point that still remains somewhat under debate is whether in severe cases it is still advisable as a rule to give bicarbonate, or whether it is preferable to wait for the combustion of the ketone acids to restore the alkali reserve.

There appears, however, to be a definite advantage, and no significant disadvantage, in retaining the assistance of alkali therapy. Even when with insulin it is possible to restore the comatose patient without alkali, it can be done quicker if the latter also is used. Campbell, a member of the Toronto group which worked out the technique of insulin therapy, is of the opinion that as quick a recovery as possible from the state of deep acidosis is desirable in order to minimize the damage which the patient accumulates from remaining in that state (4). He believes that administration of sodium bicarbonate with the insulin-glucose treatment is desirable because it accelerates the recovery. When the absorbed bicarbonate is added to that formed in the body by combustion of sodium oxybutyrate, a temporary alkali excess may result later, as shown by Cullen and Jonas (6), but apparently the alkalosis is never serious. Campbell's combination of the pre-insulin technique of alkali therapy with the modern insulin treatment appears to be well founded.

Dietary prevention of diabetic acidosis. The 4-carbon acids, hydroxybutyric and acetoacetic, are formed in the body whenever fats burn without simultaneous combustion of a sufficient amount of carbohydrate. The long fatty acid chains can be burned down to 4 carbons each, even in total diabetes when no glucose at all is burned, but further combustion of the 4-carbon oxy-acids does not occur unless accompanied by glucose oxidation. The prevention of ketosis from accumulation of these acids in diabetes becomes the problem of ascertaining how much glucose must be burned to effect combustion of the 4-carbon acids from a gram of fat, and of regulating the diet accordingly.

The first quantitative data were obtained in 1914 by Zeller (54) in experiments on normal men. He found that with one gram of carbohydrate the body could burn about 4 grams of fat without forming more than small amounts of the 4-carbon acids.

Ladd and Palmer (25, 26) later showed that diabetics also can burn fats with about one-fourth the weight of carbohydrate. Ladd and Palmer furthermore pointed out that in practicable diets it is necessary to include in the total carbohydrate the 0.6 gram of glucose which Lusk had shown to be formed from each gram of catabolized protein. In order to obtain utilization of the greatest possible number of calories by a diabetic, therefore the fat intake could be calculated from the tolerated amount of carbohydrate and protein by the following formula,

$$\text{Fat} = 4\ (\text{Carbohydrate} + 0.6\ \text{Protein})$$
$$= 4\ \text{Carbohydrate} + 2.4\ \text{Protein}$$

The quantities in the formula all refer to grams. The total caloric value for a diet so calculated is approximately 10 calories for each gram of fat. The formula indicates the combustion of approximately 2 molecules of fatty acid for 1 molecule of glucose. That diabetics could routinely ingest and burn such diets was shown by Ladd and Palmer, and independently by Woodyatt (53) and by Newburgh and Marsh (34).

Ladd and Palmer found that it was necessary to work up gradually to the full caloric intake, or severe ketosis might develop. The body requires some training on high fat diets before it develops its full fat-burning ability, expressed by the formula. Newburgh and Marsh (34) found that they could routinely start with 900 to 1000 calories and work up to 2000 or more, according to the caloric need and carbohydrate tolerance of the patient.

Woodyatt (53) and Shaffer (43) contributed much to the theory of the problem, and proposed formulae which included assumptions that the glycerine of the fat formed glucose, and that a certain amount of acetone bodies was formed from each gram of protein. However, it appears that all of the available quantitative knowledge obtained in experiments on man is expressed by the simpler formula of Ladd and Palmer.

With such a quantitative formula it became possible without insulin to construct diets of adequate caloric requirement for patients who would formerly have been kept in semi-starvation. And when insulin was given it was possible to minimize the amounts required.

NECESSITY OF DIAGNOSING ACID-BASE ABNORMALITIES BEFORE TREATMENT

Whenever regulation of the acid-base balance of the body is attempted, it should be preceded by a determination of the type and severity of the abnormality. And when an acute, rapidly changing condition, such as severe diabetic acidosis, must be handled, repeated analyses of the blood at intervals are needed in order to guide the treatment.

The methods for finding the state of the acid-base balance are now simple. The plasma bicarbonate can be determined by titration (49), or the total CO_2 content by a gasometric procedure (48) as simple as the hypobromite urea analysis. And the colorimetric plasma pH (5, 19) is hardly more difficult.

In the great majority of clinical cases the abnormality is one of alkali deficit or excess. As indicated by the paths of

these conditions in Fig. 2, plasma CO_2 or bicarbonate determination suffices for the diagnosis. Such is the case ordinarily in diabetes, nephritis, and diarrhea. Occasionally, when there is possibility of carbonic acid excess from obstructed or retarded pulmonary ventilation, or when there is possibility of carbonic acid deficit from overbreathing in fever, anoxia, or nervous conditions, it is essential to estimate also the pH. With the plasma pH and CO_2 content one can locate on a diagram such as Fig. 2 the point which indicates the nature of the acid-base change.

However, when laboratory facilities for blood analysis are not available, a simple test introduced by Palmer and Henderson (36) will often suffice to rule out alkali deficit. A slightly rounded teaspoonful of sodium bicarbonate (8-10 grams) is administered, and the urine is tested with litmus paper at half-hourly intervals for one or two hours. If the urine turns alkaline, alkali deficit can be excluded. If the urine remains acid, however, the acid-base balance may nevertheless be normal. If the alkaline reserve happens to be near the lower limit of normal, as much as 25 grams of bicarbonate may be required to turn the urine alkaline. Furthermore, in occasional pathological cases one may even give enough bicarbonate to produce an alkalosis, and the urine will still remain acid. The "bicarbonate tolerance" test is therefore valid only in one direction: if it turns the urine alkaline one may be certain that no acidosis exists. But if the urine remains acid a blood analysis must be done in order to ascertain the acid-base condition; there may or may not be an alkali deficit. A more sensitive improvement of the test has been devised by Palmer, Salvesen and Jackson (37), in which an increase of urine pH is looked for instead of development of a definitely alkaline reaction.

In a large proportion of cases in which acidosis is suspected the acid-base balance is normal, and in most such cases the urine will turn alkaline when the Palmer-Henderson alkali tolerance test is tried. Many blood analyses can therefore be dispensed with if a preliminary examination is made with this test.

Presence of even considerable amounts of acetone bodies in the urine does not necessarily indicate the existence of an internal acid deficit. I have seen a urine which turned almost black when tested with ferric chloride for acetoacetic acid, and which in fact contained 20 grams of hydroxybutyric acid per liter, and yet the acid-base point of the blood plasma was within the normal area. The case was one of toxemia of pregnancy, with anorexia and vomiting. There was the same ketosis which hunger produces in normal subjects, but the 24-hour urine volume was only 400 c.c. so that, despite its concentration in hydroxybutyric acid, it represented only about 8 grams excretion per day. Production of this amount would not cause a serious fall in the alkali reserve. In this case the acidifying effect was entirely neutralized by loss of vomited gastric hydrochloric acid. What the patient needed was not treatment for acidosis, but restoration of body fluids by salt and water, with glucose to combat the effects of starvation.

An example will indicate the consequences that may follow treatment instituted and carried on without diagnosis of the acid-base balance in the blood. A number of years ago, it was somewhat the vogue to treat pneumonia with bicarbonate, with the idea that it would ease the rapid respiration and decrease its exhausting effect. One could expect this to be the case only if the cause of the hyperpnea were alkali deficit, which, as Hastings, Neill, Morgan and Binger (18) showed, seldom occurs in pneumonia. The hyperpnea has its origin in the pulmonary changes, and not in acidification of the blood. Nevertheless the alkali treatment was administered to many patients as a routine, and one of these was referred to Binger (3) in the Hospital of the Rockefeller Institute. The patient had been apparently convalescent for several weeks, and during this time had been receiving several grams of bicarbonate daily. Nevertheless she was becoming increasingly cyanotic and dyspneic. Examination of the blood showed a state, not of acidosis, but of alkali excess, attributable to the bicarbonate therapy. The patient also had a mild chronic nephritis, with a tendency to formation of edema. The

kidneys had not been excreting the excess of bicarbonate, which had been retained and had caused the development of edema. The cyanosis was due to pulmonary edema. Both edema and cyanosis disappeared in the course of some days after alkali excess had been diagnosed and the bicarbonate administration discontinued.

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DEHYDRATION AND MEDICAL SHOCK*

DANA W. ATCHLEY

In 1831 Dr. W. B. O'Shaughnessy of Newcastle-upon-Tyne wrote a brief letter to the London Medical Gazette which embodied the results of several years of what he termed his "experimental inquiries" into the cholera. His terse summary of a physiological mechanism in terms of what we choose to call modern chemistry is a delightful contrast to the usual clinical sophistry of that day, and perhaps this, and compels me to quote his communication *in toto.*

"1. The blood drawn in the worse cases of the cholera, is unchanged in its anatomical or globular structure.

2. It has lost a large proportion of its water, 1000 parts of cholera serum having but the average of 850 parts of water.

3. It has lost also a great proportion of its *neutral* saline ingredients.

4. Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.

5. Urea exists in the cases where suppression of urine has been a marked symptom.

6. All the salts deficient in the blood, especially the alkali or carbonate of soda, are present in large quantities in the peculiar white dejected matters."

I think you will agree with a contemporary reviewer of Dr. O'Shaughnessy's "Chemical Pathology of Cholera" who in the Lancet of 1832 called particular attention to

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the "strictly logical series of deductions disfigured neither by empty hypothesis, nor by untenable and wild speculations." This same reviewer goes on to say: "This is what we want in medical reasoning. Let nothing be argued upon until it is proved; let no fact be received until its truth is established; then and not till then, will medicine rank as a science, and the disputes and cavillings of its professors become susceptible to adjustment according to exact and incontrovertible data."

Turning next to the therapeutic implications which naturally follow from the biochemical disturbances found to be present in the disease, Dr. O'Shaughnessy states that the cure is seemingly dependent upon two principles:— "First, to restore the blood to its natural specific gravity (i.e. its water content); second, to restore its deficient saline matters." He then states that, "the first of these can only be affected by absorption, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks, with sufficiently obvious modifications, apply to the second." The practical application of these principles was described as follows: "In severer cases copious enemata of warm water, holding the natural salts of the blood in solution are strongly recommended. . . . When absorption is entirely suspended the author recommends the injection into the veins of tepid water holding a solution of the normal salts of the blood." Thus it is apparent that 101 years ago a physician with an investigative and critical mind was able, with the crude methods at his disposal, to unravel the mechanism of the essential manifestation of cholera, viz. dehydration, salt depletion and shock. Furthermore, he logically employed the specific therapy indicated by such a disturbance in physiology.

Although the implications of O'Shaughnessy's brilliant work were confirmed by a number of workers at home, as well as on the continent, the struggle to overcome the traditional prejudices of those in authority is beautifully exemplified by the following words written by Dr. J. Pidduck to the London Medical Gazette, August 21, 1832.

"Turning hopelessly away from the Central Board and Local Hospital, I resolved to pursue the experiment (i.e. saline therapy) among the poor in my district, convinced that the brandy and laudanum system had been too highly recommended, and too long sanctioned by authority, to admit of the introduction by the same individuals of another system so diametrically opposed to it. Perhaps such a revolution in a cherished opinion, and a favourite practice, would be a stretch of candour and liberality almost superhuman."

In spite of the fact that in 1850 the German biochemist Karl Schmidt confirmed and greatly amplified the analytical results of O'Shaughnessy there were subsequently but occasional references to the value of intravenous salt solution. It was not until Rogers, and Nichols and Andrews in 1909 used intravenous saline injections with remarkable decrease in mortality in a cholera epidemic in the Philippine Islands that this rational form of therapy became generally accepted. I have taken time to trace the development of the chemical pathology of cholera because it presents probably the earliest instance in which there was an understanding recognition of the physiological processes involved in the development of this common complication of many disease conditions, viz. dehydration, salt depletion and shock. Furthermore, it was in the treatment of cholera that, for the first time, a rational replacement therapy was instituted with, I might add, the anticipated clinical benefit.

Chronologically the next correct appraisal of the fundamental problem may be found in the Guy's Hospital reports of 1874. Dr. C. Hilton Fagge described, therein, "A Case of Diabetic Coma, treated with partial success by the injection of a saline solution into the blood." The most impressive feature of this pioneer experiment in therapy was the rationale which he offered. This is best expressed in his own words, "What suggested to my mind the advisability of injecting a saline solution into the blood in this case was the idea that coma was due to the drain

of water from the system, caused by the diabetes. I suppose that the hypothesis upon which I acted was essentially similar to that which formed the basis of the like treatment in the collapse of cholera." The importance of this observation was nine years later overshadowed by Stadelmann's discovery of the existence of an acidosis in diabetic coma. Stadelmann quite logically felt that the replacement of alkali was the obvious point of attack. This concept so completely dominated the treatment of diabetic coma that even the more modern text books omit mention of the clear correlation between dehydration and circulatory collapse which Fagge had demonstrated in 1874. One must not neglect to state that for at least twenty-five years salt solution has been routinely employed in the treatment of diabetic acidosis. However, it was believed that the picture of low blood pressure, thready pulse, oliguria and collapse resulted from "toxic" cardiac failure rather than from shock due to decreased circulating blood volume and vasomotor paralysis. In recent years it has been shown that the loss of salts and water in diabetes is dependent upon two unrelated mechanisms. One of these is the obvious loss of base resulting from the excretion of ketone acids. The other is definitely associated with the occurrence of severe glycosuria, and may be found even in the absence of ketosis, but the nature of its underlying physiological disturbance is not known.

The clinical picture dependent upon dehydration, salt loss and consequent shock is found in many other disease conditions. Prominent among these is the group characterized by pyloric or high intestinal obstruction, as well as those patients in whom for some reason there exist fistulous openings to the upper gastro-intestinal tract or the bile ducts. It naturally follows that the picture of shock in these patients results in part at least from constant vomiting or persistent drainage of body fluids normally rich in sodium salts. It should be pointed out that in certain cases of intestinal obstruction no actual loss of salt from the body occurs, but the same result is effected by the out-

pouring of salts and water into the distended loops of intestine, thus removing it from the circulating blood and tissue spaces. The chemical changes in the blood under these conditions, viz: decreased water, sodium and chloride content and increase in urea, have been recognized for many years. Furthermore, clinicians have for a long time appreciated the therapeutic value of intravenous salt solution. The original hypothesis assumed that the condition was due to a toxemia and that the saline therapy acted as a detoxicant. It remained for Gamble, about ten years ago, to show that for pyloric obstruction, at least, no other factors than salt loss and dehydration were to be found. In other words, as in cholera and diabetic acidosis, striking clinical improvement follows the replacement of salt and water.

Another situation in which shock plays a dominant role is found in the sequelae of severe burns. Of course, we recognize that there are probably several factors which may contribute to a fatal outcome, but certainly the one which today has greatest therapeutic possibilities is that resulting from dehydration and salt depletion. Serum exudation in the burned areas is an important component of the mechanism of this dehydration. The cause of the characteristic acidosis has been ascribed to the presence of certain unknown acids, but it may possibly be due to a loss of sodium and consequently a lowering of the blood bicarbonate. However, the nature of the complicated disturbances resulting from severe burns cannot be well understood without further chemical study.

The clinical syndrome of acute adrenal insufficiency as seen in Addison's disease bears a striking resemblance to that present in the other pathological states which I have discussed. For example, weakness, prostration, rapid pulse, nausea and vomiting, fall in blood pressure, decrease in water content of the blood, increase in blood urea and decrease in the concentration of chloride and bicarbonate are characteristic. We have shown that in adrenal insufficiency in man, the sodium of the blood is markedly

lowered, as Marine and Bauman and also Zwemer had shown in cats. Furthermore, we were able to show that the administration of sodium chloride alleviates to a striking degree the clinical manifestations just described. On the other hand, it is possible to precipitate an acute and alarming attack of adrenal insufficiency by the withdrawal of salt from the diet of patients who were in relatively good clinical condition as a result of salt therapy. It is truly remarkable to observe the difference that 15 grams of salt a day will effect in the health and well-being of such a patient. It has been demonstrated in our laboratories that the decrease in salt content of the blood in adrenalectomized dogs is due to an enormous increase in the excretion of sodium by the kidney. This loss of sodium is accompanied by an augmented but not parallel water output and results in the characteristic picture of dehydration, salt depletion and shock. It seems likely that the mechanism by which salt depletion and dehydration are produced in adrenal insufficiency is different from the disturbance resulting in shock in the clinical conditions described previously. On the basis of the evidence so far accumulated we are inclined to believe that the active principle of the adrenal cortex exerts a controlling influence upon sodium metabolism through the medium of the kidney, and that the breakdown of this regulatory mechanism results in an increased rate of sodium excretion. That the regulatory effect of the adrenal cortex upon salt and water metabolism is not its sole function is proven by the fact that adrenalectomized animals eventually succumb although the period of survival may be appreciably prolonged by salt administration.

It is apparent from the foregoing discussion that the loss of water and salt from the body may occur in a variety of ways and result from a number of different physiological disturbances. Among these we have described: loss of base and water by diarrhea, vomiting or surgical drainage; loss of serum by exudation in burns; loss of salt in the urine by alterations in the carbohydrate

metabolism; loss of salt as a response to acidosis; and finally, an excessive urinary excretion of sodium in adrenal insufficiency. It might be well to add the obvious statement that the simplest form of shock resulting from salt and water depletion is that due to acute hemorrhage. There is one common denominator to be found in all of these disease conditions, when they have reached an advanced state, viz. the shock syndrome.

I should like now to consider briefly the train of events by which dehydration and salt depletion ultimately lead to the classical syndrome of shock. One of the most striking physiological principles of the body is expressed in its tenacious effort to maintain the salt content of the blood serum and the interstitial fluids at a constant level in the face of amazingly adverse circumstances. Thus, when salt is lost for any reason, the body sacrifices its precious water stores to protect its sodium concentration. Conversely, the extensive loss of water is almost invariably associated with a considerable loss of salt. Now, severe drain of salt and water from the tissue spaces is reflected in the circulating blood, producing in time a decrease in blood volume so great that the state of shock ensues in much the same manner as in acute hemorrhage. Therefore, we are led to infer that the state of shock is the physiological result of an acute disparity between the circulating blood volume and the functioning capacity of the vascular bed. This may be brought about in one of two ways; either by a relatively rapid decrease in the circulating blood volume or by sudden expansion of the vascular bed. In the clearest example of the former, viz., acute hemorrhage, the decrease in blood volume is obvious, and the ensuing results have been adequately studied. In the other conditions which I have discussed, the mechanism is analogous to hemorrhage but there are many complicating factors still to be elucidated.

Let us now turn our attention to those situations in which the state of shock is brought about primarily by a rapid dilatation of the vascular bed rather than by con-

traction of the blood volume. Since the isolation of histamine by Sir Henry Dale in 1909, physiologists have recognized that large doses of this drug will cause a generalized capillary dilatation, drop in blood pressure and collapse. Of greater importance to the clinician is a discussion of those states in which this mechanism results from natural disease processes, rather than the artificial laboratory experiment. It was my privilege some years ago to observe the clinical effect of an intravenous rattlesnake bite. This patient while extracting venom at the American Museum of Natural History was bitten on the back of his hand. In spite of the immediate administration of anti-venom serum the patient collapsed in twenty minutes and was brought to the Presbyterian Hospital. On admission he presented an extraordinary picture. His skin was cold and dusky red in color, he was semi-comatose, his respirations were shallow, his pulse was rapid and almost imperceptible, his heart sounds were inaudible and his blood pressure was too low to be read. In spite of several saline infusions and a transfusion of 700 c.c. his blood pressure, which was raised by these therapeutic procedures soon fell to a critical level again. It was not until 7200 c.c. of fluids had been given intravenously in the course of sixteen hours that his blood pressure remained normal. The almost invariably fatal outcome from an intravenous rattlesnake bite results from failure to recognize the fact that the therapeutic attack should be primarily directed against the state of shock.

When Laennec in 1826 described the weakness of the heart sounds in severe febrile conditions, he attributed this change to cardiac failure, a point of view which, unfortunately, still continues to dominate medical thought. This is true in spite of the fact that Romberg and Pässler as early as 1899 wrote upon the effect of bacterial products on the vasomotor apparatus of rabbits. These authors were able to show that a state of collapse could be induced by the intravenous injection of pneumococci or other organisms. Furthermore, they pointed out that intra-

venous salt solution was more effective in treating these animals than was subcutaneous ether, camphor, strychnine or cognac. Romberg at that time suggested the term "toxic shock" for this complication of infectious disease. It is hardly necessary to emphasize the similarity between Romberg's "toxic shock" and the shock resulting from intravenous injections of histamine or snake venom.

A striking confirmation of the shock producing capacity of the pneumococcus was afforded by a clinical experiment performed upon himself by a member of our staff a few years ago. This individual gave himself a large dose of pneumococcus vaccine, intravenously. There followed an immediate and alarming collapse during which his systolic blood pressure fell to 60 mm. of Hg. and continued below normal for three days. In conjunction with this he developed numerous petechial hemorrhages of the skin, which would lead one to infer that in addition to dilatation there had also been actual capillary damage.

Doubtless you will all recall in your own experiences with severe infectious diseases, particularly pneumonia and typhoid fever, patients who have presented the picture of falling blood pressure, rapid pulse and collapse. Certainly, in many instances this serious complication is a manifestation of shock, and probably results from an increase in the vascular bed due to capillary damage. Confusion of this state with cardiac failure will result in misdirected and possibly harmful therapy. The importance of this point of view was pointed out by Theodore Janeway in the New York State Medical Journal for 1907, when he wrote on "Some Common Misconceptions in the Pathological Physiology of the Circulation and Their Practical Significance". He said: "We must in most cases abandon the idea of cardiac death at the height of acute infectious diseases such as pneumonia, typhoid fever and septic fevers. . . . In place of heart failure we must write vasomotor failure." The discussion of this complication of infectious disease in many modern text books of medicine offers a discouraging contrast to Dr. Janeway's enlightened attitude.

Up to this point, I have discussed the occurrence of shock in a variety of clinical conditions, stressing in each instance the mechanism which predominates the picture. In some of these situations shock resulted primarily from a rapid decrease in circulating blood volume, whereas in others the chief factor was vasodilatation. However, I think it is only fair to state that this is a diagrammatic visualization of processes which like other biological phenomena are more complex than I have seemed to indicate. For example, in histamine shock, although the primary disturbance is admittedly due to capillary dilatation, nevertheless capillary dilatation is almost inevitably accompanied by an increase in the size of the capillary pores which permits large quantities of blood serum to escape into the tissue spaces. Thus, the component of decreased circulating blood volume also plays a part. This effect may naturally be assumed to exist in the case of snake venom and bacterial capillary poisoning, or in any other condition in which generalized capillary dilatation is marked.

In diabetic acidosis accompanied by the shock syndrome, I have indicated the importance of dehydration and salt depletion. We have all seen patients in whom the state of shock has persisted after adequate replacement therapy and after the ketosis had disappeared. There is experimental evidence which suggests that there may be in these cases a factor of capillary poisoning which is responsible for the persistent recurrence of the shock syndrome. It has been shown that certain substances which have a chemical similarity to the ketone bodies, for example, acetyl acetone and sodium acetate, will produce vasodilatation in animals.

There has been much discussion of the participation of a toxin in the production of the clinical manifestations of intestinal obstruction and, indeed, substances with histamine-like action have been isolated from damaged loops of gut. To what extent these substances contribute to the total mechanism in producing shock is still problematical.

I have pointed out the role of dehydration and salt loss in severe burns but here, too, certain toxic substances are perhaps absorbed from the necrosing tissue and may act as capillary poisons.

It seems possible that there is still another mechanism involved in the production of shock through vasodilatation, though our understanding of the process is still obscure. I am referring to the influence of the sympathetic nervous system. This is dramatically demonstrated in the production of traumatic shock. Although severe and extensive traumatization of tissue results in a certain amount of dehydration by serous exudation and hemorrhage, it has been reported that injury to a limb isolated from the rest of the body except for its nerve supply may result in shock. Thus it would appear possible to induce shock without the aid of salt loss, dehydration or circulating toxin. In the field of internal medicine, it is recognized that one of the immediate effects of extensive infarction of the myocardium is a clinical picture of falling blood pressure and collapse, which is similar to, if not identical with shock. It is hard to believe that such a rapidly developing syndrome could result from tissue damage and it seems likely that it is brought about through a reflex nervous mechanism. Obviously, the development of shock in cardiac infarction is a fortunate physiological disturbance and hence should not be treated as in other conditions.

Before proceeding to the discussion of therapy, I should like to enumerate briefly a few of the systemic effects of shock. The most significant effect is the interference with tissue function which results from circulatory stasis and diminished blood supply. No organ shows this disturbance more strikingly than does the kidney. Renal function is compromised and anuria frequently results. This, in turn, definitely upsets the acid-base equilibrium of the body and in the case of diabetic shock prevents the excretion of ketone bodies, thus adding to the seriousness of the disease state. The tissues of the central nervous system are also

included in the general damage and the resulting pathology doubtless plays a large part in the terminal stages.

The treatment of shock is more or less independent of its cause. Whether it be due to trauma, toxemia, hemorrhage or dehydration, the physiological problem is the same; namely, a disparity between the circulating blood volume and the vascular bed. On one hand there is primarily a decreased blood volume from hemorrhage or fluid loss; on the other, an increased vascular bed resulting from capillary dilatation. The need for immediate measures to increase the circulating blood volume is common to all types.

I think it is fair to say that the longer the state of shock is permitted to exist, the more difficult it becomes to alleviate it and the higher is the mortality. Consequently, delay in initiating therapy is dangerous. As an emergency method, the intravenous injection of 50 c.c. of 50 per cent glucose, which may be conveniently kept on hand, is of some temporary value, as it will draw fluid into the blood stream from the tissue spaces. Its action is fleeting and it should be followed promptly by the intravenous injecton of 1000 to 2000 c.c. of normal salt solution. This procedure may be repeated within two or three hours without any danger to the myocardium. The response of the blood pressure is the best indication for such repetition. The value of salt solution in the treatment of shock developing in the course of infectious diseases has not been thoroughly tested, and final conclusions as to its usefulness are still uncertain. In shock due to other causes, dramatic results follow this therapeutic measure.

The ideal treatment for shock is a large blood transfusion, and every patient likely to develop shock should have his blood grouped early in the course of his disease. When salt solution fails, transfusion may turn the tide. The theoretical basis for the fact that blood is more effective than salt solution lies in the assumption that it contains a nondiffusible substance, i.e., serum protein, which

makes the influence of added blood a more permanent one. One cannot accept this suggestion without caution, for it has been clearly proved that in histamine shock whole serum leaves the blood stream; in other words, the capillaries become readily permeable to protein. However, there is no denying the greater therapeutic value of blood over all other fluids. In an attempt to find a substitute for blood, numerous colloidal substances have been tried. The most prominent of these is acacia. During the World War, this solution was tried and given up because of the severe reactions which frequently followed its administration. In the past two or three years, methods of preparation of acacia solutions have been improved, and while enthusiastic reports from its action have appeared, it is too early to recommend its general use.

It is obvious that all therapy in shock should be intravenous rather than subcutaneous or intramuscular. The rapidity of response is much greater when the intravenous route of administration is employed, because the poor peripheral circulation slows subcutaneous absorption tremendously. This applies to hypodermic medication as well as to fluid administration.

The use of vasoconstrictors, such as epinephrine, is not helpful and may, indeed, be dangerous. From a physiologic standpoint they are contraindicated because the blood vessels which they affect are already constricted to the disadvantage of the capillary circulation, as has been shown by studies of both the skin and visceral arterioles. There has been much mention of heat loss as a contributing cause of shock and it is consequently essential to keep the patient as warm as possible.

In conclusion I should like to say that while most of what I have had to tell you this evening is an old story, I feel that it is a story worth retelling because there is no doubt that the importance of the state of shock, particularly as it occurs in the field of internal medicine, has not received its just and proper emphasis.

PROCEEDINGS OF ACADEMY MEETINGS

FEBRUARY

STATED MEETINGS

Program arranged in cooperation with the SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE—February 1

I. EXECUTIVE SESSION—a. Reading of the Minutes; b. Election of Fellows and Members.
II. PAPERS OF THE EVENING—*Symposium: present status of the rheumatic fever problem*—a. Certain aspects of the pathology of rheumatic fever, W. C. Von Glahn; b. Clinical history of rheumatic fever and observations relating to etiology, T. Duckett Jones, Boston; c. Current conceptions of the nature of the disease, Homer F. Swift; d. Discussion, Louis Gross, John Paul, New Haven, A. Dochez, John Wyckoff.

THE HARVEY SOCIETY (IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE) February 15

THE FIFTH HARVEY LECTURE, "The Clinical Application of Some Recent Knowledge of the Biliary Tract and of the Pancreas," Evarts A. Graham, Professor of Surgery, Washington University School of Medicine, St. Louis.

SECTION MEETINGS

SECTION OF SURGERY—February 2

I. PRESENTATION OF CASES—a. 1. Traumatic rupture of the common hepatic duct—2½ year result—2. Embryonal carcinoma of the testicle; orchidectomy with high ligation of the cord; deep X-ray therapy; 6 year result—3. Recurrent dislocation of the shoulder; Nicola operation; 2 year result, Kenneth M. Lewis; b. 1. Second acute perforation of marginal ulcer—2. Mikulicz operation on jejunum, Edward Victor Denneen.
II. PAPERS OF THE EVENING—a. The liver function test in cholecystectomy, Condict W. Culter; b. Acute cholecystitis. A study of 75 proven cases with subsiding or subsided clinical manifestations at time of operation, Arthur S. W. Touroff.
III. GENERAL DISCUSSION—Seward Erdman, Joshua E. Sweet, Frederic W. Bancroft.
IV. EXECUTIVE SESSION.

SECTION OF DERMATOLOGY AND SYPHILOLOGY—February 6

I. PRESENTATION OF CASES—From The Mount Sinai Hospital.
II. PRESENTATION OF MISCELLANEOUS CASES.
III. DISCUSSION OF SELECTED CASES. IV. EXECUTIVE SESSION.

JOINT MEETING—SECTION OF NEUROLOGY AND PSYCHIATRY *and the* SECTION OF MEDICINE—February 13

I. PAPER OF THE EVENING—The psychogenic origin of organic disease, Eli Moschcowitz.
II. ILLUSTRATIVE CASE PRESENTATIONS—a. From Mount Sinai Hospital, B. S. Oppenheimer, Solomon Silver (by invitation); b. From Presbyterian Hospital, George Draper; c. From New York Hospital, Ephraim Shaw (by invitation), George W. Henry (by invitation). III. GENERAL DISCUSSION.

SECTION OF ORTHOPEDIC SURGERY—February 16

I. PRESENTATION OF CASES—a. 1. A case presenting fracture of lumbar spine, os calcis, and carpal scaphoid, Martin W. Ware—2. Fracture of fibula—adhesive plaster dressing and immediate weight-bearing, Arthur Krida; b. 1. Fracture dislocation of elbow with resection—end result—2. Fracture and complete dislocation of lumbar vertebrae, Richmond Stephens, Raymond Lewis; c. Dislocation of the head of the astragalus—open reduction, Frank S. Child (by invitation).
II. PAPER OF THE EVENING—Some physiological considerations concerning fracture healing, Robert W. Johnson, Baltimore (by invitation).
III. DISCUSSION—Fred H. Albee, Clay Ray Murray, John J. Moorhead.

SECTION OF OPHTHALMOLOGY—February 19

I. INSTRUCTION HOUR, 7 to 8 o'clock—Ophthalmoscopy, Arthur J. Bedell.

II. DEMONSTRATION HOUR, 7:30 to 8:30 o'clock—a. Slit lamp studies, Milton L. Berliner, Isadore Goldstein, Wendell L. Hughes, Girolamo Bonaccolto (by invitation); b. Many cases with ocular fundus lesions; c. Binocular and hand ophthalmoscopes, Mr. Fairbain, Colonial Optical Co. (by invitation).

III. SECTION MEETING, 8:30 to 10:30 o'clock—a. Reading of the minutes; b. Case reports: 1. A case of choroidal atrophy without night blindness, Isaac Hartshorne—2. A case of Coate's disease, Richard T. Paton (by invitation)—3. Pathology of these retinal lesions, Bernard Samuels, projection by Edgar Burchell, M. Sc. (by invitation); c. Scientific paper: 1. Hereditary and familial degeneration of the macula, Ralph I. Lloyd; Discussors: 1. Henry H. Tyson, 2. Conrad Berens.

SECTION OF GENITO-URINARY SURGERY—February 21

I. SCIENTIFIC PROGRAM FROM THE UROLOGICAL DEPARTMENT OF THE MORRISANIA CITY HOSPITAL—a. Urological staff organization at Morrisania City Hospital, C. Travers Stepita; b. Perforation of ureter by a calculus. A case report, Succorso A. Suriano (by invitation); c. Gangrenous cystitis eventuating in cystotomy. A case report, Maximillian Zigler (by invitation); d. Silent renal and ureteral calculi. With lantern slide demonstration, Joseph Schwartz; e. Recto-urethral fistula with involvement of seminal vesicle. Demonstration of patient, John W. Rogers (by invitation); f. Traumatic rupture of solitary kidney. A case report, John Roth (by invitation); g. Electrosurgery in urology, Daniel A. Sinclair (by invitation); h. Unusual tumor of adrenal with destruction of kidney. A case report, J. J. Valentine; Discussion to be opened by William Aronson (by invitation); i. Branching calculus and hypernephroma of kidney. A case report, Angel F. Golderos (by invitation); j. Perinephritic inflammations and suppurations, John Duff; k. A review of prostatic surgery at Morrisania City Hospital, 1930-1933, John Toole.

COMBINED MEETING OF THE SECTION OF OTOLARYNGOLOGY *and the* SECTION OF PEDIATRICS—February 21

I. CASE PRESENTATION—Two cases of pharyngeal hematoma and hemorrhage, William Spielberg.

II. PAPERS OF THE EVENING—a. Hematoma and hemorrhage of the pharynx and peritonsillar area, Samual Salinger, Chicago (by invitation); b. Progress in tonsil surgery, illustrated by slides and motion pictures, a resume of 25,000 cases, Robert H. Fowler; c. Personal observations on the after-effects of tonsillectomy, Murray H. Bass, Howard H. Mason; d. Practical considerations of diseases of the nasal accessory sinuses in children, William Mithoefer, Cincinnati (by invitation); Discussion opened by Herman Schwarz, Charles J. Imperatori.

III. GENERAL DISCUSSION. IV. EXECUTIVE SESSION.

SECTION OF OBSTETRICS AND GYNECOLOGY—February 27
Program arranged by the Obstetrical Staff of the Fifth Avenue Hospital

I. PRESENTATION OF CASES—Preventative pre-natal treatment of melena neonatorum in successive pregnancies, John E. Tritsch (by invitation); Discussion to be opened by I. Newton Kugelmass (by invitation).

II. PAPERS OF THE EVENING—a. Dysmenorrhea in industry, Frances E. Shields (by invitation); Discussion to be opened by Emily D. Barringer; b. Some urethral conditions in women (lantern slides), H. Dawson Furniss; Discussion to be opened by Sophie Kleegman, E. Barringer; c. Present status of obstetric anesthesia, analgesia and amnesia, Leon S. Loizeaux; Discussion to be opened by T. Drysdale Buchanan (by invitation), Paul N. Wood.

III. GENERAL DISCUSSION. IV. EXECUTIVE SESSION.

AFFILIATED SOCIETIES

NEW YORK ROENTGEN SOCIETY *in affiliation with* THE NEW YORK ACADEMY OF MEDICINE—February 19

I. 8:00 to 8:30 p. m.—Demonstration and discussion of interesting cases.

II. 8:30 p. m.—Symposium on indications for roentgentherapy in malignant disease of the ear, nose and throat; Presentation of cases, Maurice Lenz (previously shown to this society) (30 minutes); Microscopic structure, A. P. Stout; Cancer of the nose, A. A.

Schwartz; Cancer of the ear, J. D. Kernan; Cancer of the larynx, R. E. Buckley; Cancer of the oropharynx, including cervical gland metastasis, G. H. Semken (10 minutes each); Discussion to be opened by Francis C. Wood, Hayes E. Martin, A. L. L. Bell. All cases will be available for examination at 8:00 o'clock.

III. General Discussion. IV. Executive Session.

NEW YORK MEETING OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE *under the auspices of* THE NEW YORK ACADEMY OF MEDICINE—February 21

I. Changes in the hypopthysis of adult male and female rats after prolan injection, A. E. Severinghaus.

II. Reduction of methylene blue by the blood of young infants, Carl H. Smith.

III. Therapeutic type VIII (Cooper) serum: its efficiency and reactions, J. G. M. Bullowa.

IV. A type-specific substance from the meningococcus, H. W. Scherp, G. Rake.

V. Chemical studies in bacterial agglutination. I. A micro method for the quantitative estimation of agglutinins, M. Heidelberger, E. A. Kabat.

VI. Bacterial variation in pneumococcus and streptococcus hemolyticus, M. H. Dawson; Introduced by A. R. Dochez.

VII. Anaphylactogenic properties of purified milk proteins, raw, evaporated, superheated, dried and acidified milk, B. Ratner, H. L. Gruehl.

VIII. Metallic glutamates in nutritional anemia, E. Brand, C. J. Stucky.

IX. Specificity of enhancing material from mammalian tumors, A. E. Casey.

NEW YORK PATHOLOGICAL SOCIETY *in affiliation with* THE NEW YORK ACADEMY OF MEDICINE—February 22

I. Demonstration of Pathological Specimens.

II. Papers of the Evening—a. Allergic inflammation of the lungs, B. M. Fried (by invitation); b. Dilatation of the pulmonary artery, (a) Idiopathic, (b) Associated with congenital cardiac anomalies, B. S. Oppenheimer; c. Dermatomyositis: a report of two cases, Sigmund Wilens (by invitation), Abner Wolf (by invitation); d. Giant cell leukemia, Paul Klemperer.

III. Executive Session.

LIBRARY NOTES

Recent Accessions to the Library

Beckman, H. Treatment in general practice. 2 ed.
Phil., Saunders, 1934, 889 p.

Dandy, W. E. Benign tumors in the third ventricle of the brain.
Springfield, Ill., Thomas, [1933], 171 p.

Falk, H. C. Operating room procedure for nurses and internes. [2. ed.].
N. Y., Putnam, 1934, 413 p.

Fishberg, A. M. Hypertension and nephritis. 3. ed.
Phil., Lea, 1934, 668 p.

Frazer, (Sir) J. G. The fear of the dead in primitive religion.
London, Macmillan, 1933, 204 p.

Globus, J. H. Neuroanatomy. 6. ed.
Balt., Wood, 1934, 240 p.

Grinker, R. R. Neurology.
Springfield, Ill., Thomas, [1934], 979 p.

Halliburton, W. D. & McDowall, R. J. S. Handbook of physiology. 33. ed.
Phil., Blakiston, [1934], 971 p.

Nicholson, D. Laboratory medicine. 2. ed.
Phil., Lea, 1934, 566 p.

Ray, M. B. Rheumatism in general practice.
London, Lewis, 1934, 404 p.

Rose, (Mrs.) M.D. (Swartz). The foundations of nutrition. Revised ed.
N. Y., Macmillan, 1933, 630 p.

Seldin, H. M. Practical anesthesia for dental and oral surgery.
Phil., Lea, 1934, 525 p.

Stannus, H. S. A sixth venereal disease.
London, Baillière, 1933, 270 p.

Tuffier, T. Titres et travaux scientifiques.
Paris, Jouve, 1933, 290 p.

Whitnall, S. E. The study of anatomy. 2. ed.
London, Arnold, 1933, 93 p.

Books by Fellows

More than ever, we need gifts of books for the Library, as our funds are much decreased. The Library Committee would be very pleased if all Fellows would present copies of their newly published works to the Academy. Many have been kind in this way in the past, and the Library Committee offers them its sincere thanks.

FELLOWS AND MEMBERS ELECTED FEBRUARY 1, 1934

FELLOWS

Roland I. Grausman ..... 130 West 58 Street
Louis Charles Rosenberg ..... 11 Murray Street, Newark, N. J.

MEMBERS

Myron A. Sallick ..... 1125 Park Avenue
Louis H. Barenberg ..... 1749 Grand Concourse
Arthur S. Calman ..... 1160 Park Avenue
Coleman B. Rabin ..... 1233 Park Avenue
John Alfred O'Regan ..... 983 Park Avenue
Janet Travell ..... 9 West 16 Street

DEATHS OF FELLOWS OF THE ACADEMY

DENNIS, FREDERIC SHEPARD, M.D., 1136 Fifth Avenue, New York City; graduated in medicine from Bellevue Hospital Medical College in 1874; elected a Fellow of the Academy May 1, 1879; died March 8, 1934. Dr. Dennis was a Fellow of the American Medical Association and a member of the County and State Medical Societies. He was a Fellow of the Royal College of Surgeons and the American College of Surgeons; a member of the Clinical Society of London, the German Congress of Surgeons and a member and former president of the American Surgical Association. For twelve years he was Professor of Clinical Surgery at Cornell Medical College and held the same chair at Bellevue Hospital Medical College from 1883 to 1898. Dr. Dennis was one of the first surgeons in the United States to demonstrate the Lister Theory of Antisepsis. He was one of the founders of Harlem Hospital and at the time of his death was Consulting Surgeon to Bellevue, St. Vincent's, Montefiore and Litchfield County hospitals.

LAMBERT, FREDERICK ELLSWORTH, M.D., 157 Ocean Avenue, Jersey City, New Jersey; graduated in medicine from the Long Island Hospital Medical College, Brooklyn, New York, in 1894; elected a Fellow of the Academy April 4, 1907; died, March 1, 1934. Dr. Lambert was a Fellow of the American Medical Association and a member of the County and State Medical Societies. He was Attending Physician to Christ Hospital in Jersey City.

SPAULDING, EDITH ROGERS, M.D., 103 East 86 Street, New York City; graduated in medicine from Tufts College Medical School, Boston, in 1909; elected a Fellow of the Academy February 3, 1921; died February 23, 1934. Dr. Spaulding was a Fellow of the American Medical Association, a member of the County and State Medical Societies, the American Psychiatric Association, the American Psychopathological Association, the Neurological Society, the New York Society for Clinical Psychiatry and the Psychoanalytical Society of New York. She was Assistant Psychiatrist to Vanderbilt Clinic.

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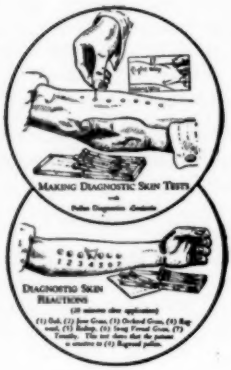

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